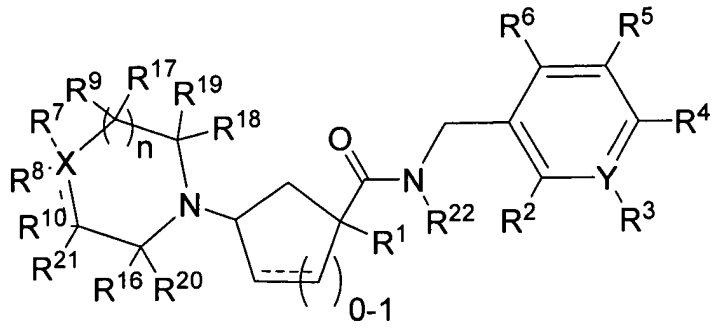
Amendments to the Claims

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims

1. (currently amended) A compound of Formula I:



I

wherein:

~~X is C, N, O, S or SO_2;~~ X is C;

~~Y is N or C;~~ Y is N;

R^1 is selected from: hydrogen, $-SO_2R^{14}$, $-C_{0-3}$alkyl-$S(O)R^{14}$, $-SO_2NR^{12}R^{12}$, $-C_{1-6}$alkyl, $-C_{0-6}$alkyl-O-C_{1-6}alkyl, $-C_{0-6}$alkyl-S-C_{1-6}alkyl, -(C_{0-6}alkyl)-(C_{3-7}cycloalkyl)-(C_{0-6}alkyl), hydroxy, heterocycle, -CN, $-NR^{12}R^{12}$, $-NR^{12}COR^{13}$, $-NR^{12}SO_2R^{14}$, $-COR^{11}$, $-CONR^{12}R^{12}$, and phenyl,

where said alkyl and said cycloalkyl are unsubstituted or substituted with 1-7 substituents independently selected from: halo, hydroxy, -O-C_{1-3}alkyl, trifluoromethyl, C_{1-3}alkyl, -O-C_{1-3}alkyl, -COR^{11}, -SO_2R^{14}, -$NHCOCH_3$, -$NHSO_2CH_3$, -heterocycle, =O, and -CN,

where said phenyl and said heterocycle are unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl;

R^2 is selected from: hydrogen, C_{1-3}alkyl unsubstituted or substituted with 1-3 fluoro, -O-C_{1-3}alkyl unsubstituted or substituted with 1-3 fluoro, hydroxy, chloro, fluoro, bromo, phenyl and heterocycle;

~~R^3 is selected from: hydrogen, hydroxy, halo, C_{1-3}alkyl unsubstituted or substituted with 1-6 substituents independently selected from fluoro, hydroxy, and -COR^{11}, -$NR^{12}R^{12}$, -COR^{11}, -$CONR^{12}R^{12}$, -$NR^{12}COR^{13}$, -$OCONR^{12}R^{12}$, -$NR^{12}CONR^{12}R^{12}$, -heterocycle, -CN, -NR^{12}-SO_2-$NR^{12}R^{12}$, -NR^{12}-SO_2-R^{14}, -SO_2-$NR^{12}R^{12}$ and nitro, when Y is C; or~~

~~R^3 is oxygen or is absent, when Y is N;~~ R^3 is oxygen or is absent;

R^4 is selected from: hydrogen, C_{1-6}alkyl, trifluoromethyl, trifluoromethoxy, chloro, fluoro, bromo, and phenyl;

R^5 is selected from: C_{1-6}alkyl unsubstituted or substituted with one or more substituents selected from 1-6 fluoro and hydroxyl, -O-C_{1-6}alkyl unsubstituted or substituted with 1-6 fluoro, -CO-C_{1-6}alkyl unsubstituted or substituted with 1-6 fluoro, -S-C_{1-6}alkyl unsubstituted or substituted with 1-6 fluoro, -pyridyl unsubstituted or substituted with one or more substituents selected from halo, trifluoromethyl, C_{1-4}alkyl and COR^{11}, fluoro, chloro, bromo, -C_{4-6}cycloalkyl, -O-C_{4-6}cycloalkyl, phenyl unsubstituted or substituted with one or more substituents selected from halo, trifluoromethyl, C_{1-4}alkyl and COR^{11}, -O-phenyl unsubstituted or substituted with one or more substituents selected from halo, trifluoromethyl, C_{1-4}alkyl and

COR^{11}, -C_{3-6}cycloalkyl unsubstituted or substituted with 1-6 fluoro, -O-C_{3-6}cycloalkyl unsubstituted or substituted with 1-6 fluoro, -heterocycle, -CN and -COR^{11};

R^6 is selected from: hydrogen, C_{1-6}alkyl, trifluoromethyl, fluoro, chloro and bromo;

~~R^7 is nothing when X is -O-, -S-, or -SO_2-;~~

R^7 is selected from: hydrogen, (C_{0-6}alkyl)-phenyl, (C_{0-6}alkyl)-heterocycle, (C_{0-6}alkyl)-C_{3-7}cycloalkyl , (C_{0-6}alkyl)-COR^{11}, (C_{0-6}alkyl)-(alkene)-COR^{11}, (C_{0-6}alkyl)-SO_3H, (C_{0-6}alkyl)-W-C_{0-4}alkyl, (C_{0-6}alkyl)-$CONR^{12}$-phenyl and (C_{0-6}alkyl)-$CONR^{15}$-V-COR^{11}, ~~when X is C or N;~~

where V is selected from C_{1-6}alkyl and phenyl,

where W is selected from: a single bond, -O-, -S-, -SO-, -SO_2-, -CO-, -CO_2-, -$CONR^{12}$- and –NR^{12}-,

where said C_{0-6}alkyl is unsubstituted or substituted with 1-5 substituents independently selected from: halo, hydroxy, -C_{0-6}alkyl, -O-C_{1-3}alkyl, trifluoromethyl and -C_{0-2}alkyl-phenyl,

where said alkene is unsubstituted or substituted with 1-3 substituents independently selected from: halo, trifluoromethyl, C_{1-3}alkyl, phenyl and heterocycle;

where said phenyl, heterocycle, cycloalkyl and C_{0-4}alkyl are independently unsubstituted or substituted with 1-5 substituents independently selected from: halo, trifluoromethyl, hydroxy, C_{1-6}alkyl, -O-C_{1-3}alkyl, -C_{0-3}-COR^{11}, -CN, -$NR^{12}R^{12}$, -$CONR^{12}R^{12}$ and -C_{0-3}-heterocycle,

or where said phenyl and heterocycle are fused to another heterocycle, which itself may be unsubstituted or substituted with 1-2 substituents independently selected from hydroxy, halo, -COR^{11}, and –C_{1-4}alkyl;

R^8 is selected from: hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyl-hydroxy, -O-C_{1-3}alkyl, -COR^{11}, -$CONR^{12}R^{12}$ and –CN, ~~when X is C, or;~~ or

R^8 is nothing ~~when X is O, S, SO_2 or N, or~~ when a double bond joins the carbons to which R^7 and R^{10} are attached;

or R^7 and R^8 are joined together to form a ring which is selected from: 1H-indene, 2,3-dihydro-1H-indene, 2,3-dihydro-benzofuran, 1,3-dihydro-isobenzofuran, 2,3-dihydro-benzothiofuran, 1,3-dihydro-isobenzothiofuran, 6*H*-cyclopenta[*d*]isoxazol-3-ol, cyclopentane and cyclohexane,

where said ring is unsubstituted or substituted with 1-5 substituents independently selected from: halo, trifluoromethyl, hydroxy, C_{1-3}alkyl, -O-C_{1-3}alkyl, -C_{0-3}-COR^{11}, -CN, -$NR^{12}R^{12}$, -$CONR^{12}R^{12}$ and -C_{0-3}-heterocycle;

R^9 and R^{10} are independently selected from: hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyl-COR^{11}, C_{1-6}alkyl-hydroxy, -O-C_{1-3}alkyl, =O when R^9 or R^{10} is connected to the ring via a double bond and halo;

or R^7 and R^9, or R^8 and R^{10}, are joined together to form a ring which is phenyl or heterocycle,

where said ring is unsubstituted or substituted with 1-7 substituents independently selected from: halo, trifluoromethyl, hydroxy, C_{1-3}alkyl, -O-C_{1-3}alkyl, -COR^{11}, -CN, -$NR^{12}R^{12}$ and -$CONR^{12}R^{12}$;

R^{11} is independently selected from: hydroxy, hydrogen, C_{1-6} alkyl, -O-C_{1-6}alkyl, benzyl, phenyl, C_{3-6} cycloalkyl,

where said alkyl, phenyl, benzyl or cycloalkyl group is unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, $-CO_2H$, $-CO_2-C_{1-6}$ alkyl, and trifluoromethyl;

R^{12} is selected from: hydrogen, C_{1-6} alkyl, benzyl, phenyl and C_{3-6} cycloalkyl,

where said alkyl, phenyl, benzyl or cycloalkyl group is unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, $-CO_2H$, $-CO_2-C_{1-6}$ alkyl and trifluoromethyl;

R^{13} is selected from: hydrogen, C_{1-6} alkyl, $-O-C_{1-6}$alkyl, benzyl, phenyl and C_{3-6} cycloalkyl,

where said alkyl, phenyl, benzyl or cycloalkyl group is unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, $-CO_2H$, $-CO_2-C_{1-6}$ alkyl, and trifluoromethyl;

R^{14} is selected from: hydroxy, C_{1-6} alkyl, $-O-C_{1-6}$alkyl, benzyl, phenyl andC_{3-6} cycloalkyl,

where said alkyl, phenyl, benzyl or cycloalkyl group is unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy, $-CO_2H$, $-CO_2-C_{1-6}$ alkyl and trifluoromethyl;

R^{15} is hydrogen or C_{1-4}alkyl, or R^{15} is joined via a 1-5 carbon tether to one of the carbons of V to form a ring;

R^{17}, R^{19}, R^{20} and R^{21} are independently selected from: hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyl-COR^{11}, C_{1-6}alkyl-hydroxy, $-O-C_{1-3}$alkyl, trifluoromethyl and halo;

~~R^{16} and R^{18} are independently selected from: hydroxy, C_{1-6}alkyl, C_{1-6}alkyl-COR^{11}, C_{1-6}alkyl-hydroxy, -O-C_{1-3}alkyl and halo,~~

~~where said alkyl is unsubstituted or substituted with 1-6 substituents independently selected from fluoro and hydroxyl;~~

~~or~~ R^{16} and R^{18} together form a bridge consisting of -C_{1-4}alkyl-, -C_{0-2}alkyl-O-C_{1-3}alkyl- or –C_{1-3}alkyl-O-C_{0-2}alkyl-, where said alkyl is unsubstituted or substituted with 1-2 substituents independently selected from: oxy where the oxygen is joined to said bridge via a double bond, fluoro, hydroxy, methoxy, methyl and trifluoromethyl;

R^{22} is selected from: hydrogen, phenyl, C_{1-6}alkyl which is substituted or unsubstituted with 1-6 substituents selected from: -COR^{11}, hydroxy, fluoro, chloro and -O-C_{1-3}alkyl;

or R^2 and R^{22} together are a linker, forming a heterocycle ring, said linker selected from (with the left side of the linker being bonded to the amide nitrogen at R^{22}): -$CH_2(CR^{23}R^{23})_{1-3}$-, -$CH_2$-$NR^{24}$-, -$NR^{12}$-$CR^{23}R^{23}$-, -$CH_2O$-, -$CH_2SO_2$-, -$CH_2SO$-, -$CH_2S$-, -$CR^{23}R^{23}$-;

R^{23} is independently selected from: hydrogen, C_{1-3}alkyl unsubstituted or substituted with 1-6 substituents independently selected from fluoro and hydroxy, COR^{13}, SO_2R^{14}, $SO_2NR^{12}R^{12}$, hydroxy, halo, -$NR^{12}R^{12}$, -COR^{11}, -$CONR^{12}R^{12}$, -$NR^{12}COR^{13}$, -$OCONR^{12}R^{12}$, -$NR^{12}CONR^{12}R^{12}$, -heterocycle, -CN, -NR^{12}-SO_2-$NR^{12}R^{12}$, -NR^{12}-SO_2-R^{14}, and -SO_2-$NR^{12}R^{12}$;

or one R^{23} is =O and the other R^{23} is absent;

where R^{24} is selected from: hydrogen, C_{1-3}alkyl where said alkyl is unsubstituted or substituted with 1-6 substituents independently selected from fluoro and hydroxy, COR^{13}, SO_2R^{14} and $SO_2NR^{12}R^{12}$;

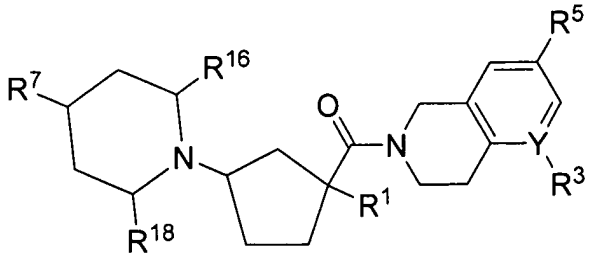
n is selected from 0, 1 and 2;

the dashed line represents an optional bond;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

2. (canceled)

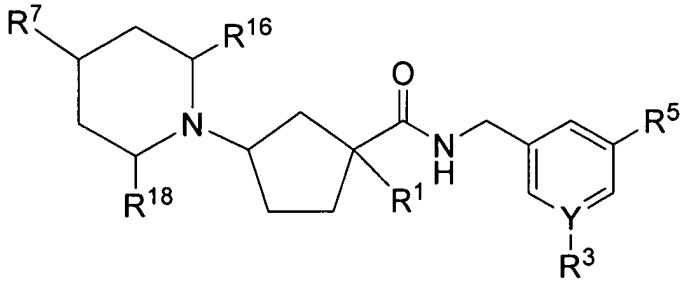
3. (original) The compound of claim 1 of the Formula Ia:



Ia

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

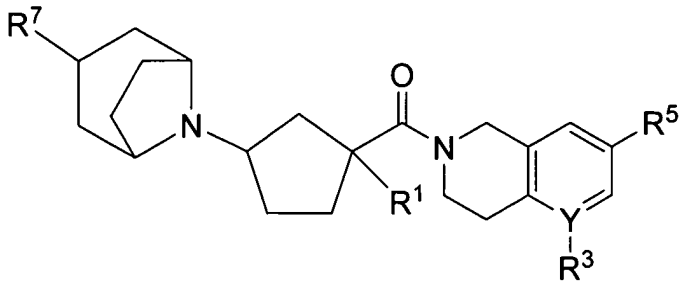
4. (original) The compound of claim 1 of the Formula Ib:



Ib

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

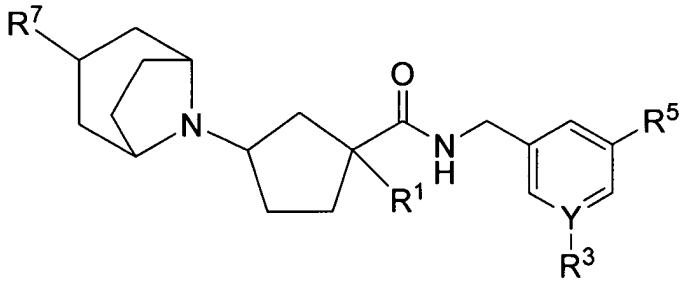
5. (original) The compound of claim 1 of the Formula Ic:



Ic

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

6. (original) The compound of claim 1 of the Formula Id:



Id

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

7. (original) The compound of claim 1, wherein R^1 is C_{1-6}alkyl, unsubstituted or substituted with hydroxyl or 1-6 fluoro, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

8. (original) The compound of claim 6, wherein R^1 is selected from: -$CH(CH_3)_2$, -$CH(OH)CH_3$ and -CH_2CF_3, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

9. (original) The compound of claim 1, wherein R^2 is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

10. (original) The compound of claim 1, wherein R^2 is connected to R^{22} by $-CH_2-CH_2-$, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

11. (currently amended) The compound of claim 1, ~~wherein, when Y is N,~~ wherein R^3 is absent, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

12. (currently amended) The compound of claim 1, ~~wherein, when Y is N,~~ wherein R^3 is O, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

13-14. (canceled)

15. (original) The compound of claim 1, wherein R^4 is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

16. (original) The compound of claim 1, wherein R^5 is selected from: C_{1-6}alkyl substituted with 1-6 fluoro, -O-C_{1-6}alkyl substituted with 1-6 fluoro, chloro, bromo and phenyl, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

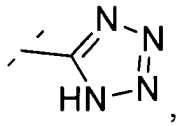
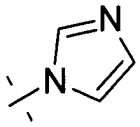
17. (original) The compound of claim 15, wherein R^5 is trifluoromethyl, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

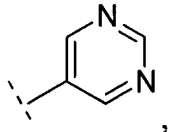
18. (original) The compound of claim 1, wherein R^6 is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

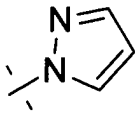
19. (original) The compound of claim 1, wherein R^7 is phenyl, heterocycle, C_{3-7}cycloalkyl, C_{1-6}alkyl, $-COR^{11}$ or -CONH-V-COR^{11}, where V is C_{1-6}alkyl or phenyl, where said phenyl, heterocycle, C_{3-7}cycloalkyl and C_{1-6}alkyl are unsubstituted or substituted with 1-5 substituents independently selected from: halo, trifluoromethyl, hydroxy, C_{1-3}alkyl, -O-C_{1-3}alkyl, -COR^{11}, -CN, -heterocycle and -$CONR^{12}R^{12}$, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

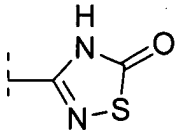
20. (original) The compound of claim 1, wherein R^7 is phenyl, heterocycle, C_{1-4}alkyl, $-COR^{11}$, and -CONH-V-COR^{11}, where V is selected from C_{1-6}alkyl or phenyl, and where the phenyl, heterocycle, and C_{1-4}alkyl is unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C_{1-3}alkyl, -O-C_{1-3}alkyl, -COR^{11} and –heterocycle, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

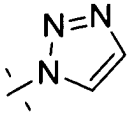
21. (currently amended) The compound of claim 1, wherein, ~~when X is C,~~ R^7 is selected from:

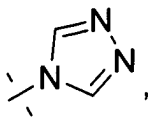

,

,

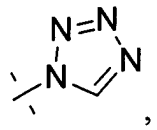
para-fluorophenyl,

,

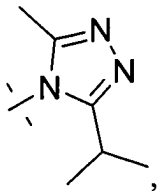
3-carboxyphenyl,

,

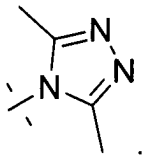
3-carboxy-4-fluorophenyl,

,

phenyl,

,

-$CO_2CH_2CH_3$,  ,

-CO_2H,  ,

-$CONHCH_3$,  ,

-hydroxy, and  .

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

22. (currently amended) The compound of claim 1, wherein, ~~when X is C,~~ R^8 is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

23. (original) The compound of claim 1, wherein R^9 and R^{10} are hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

24. (canceled)

25. (original) The compound of claim 1, wherein R^{17} is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

26. (canceled)

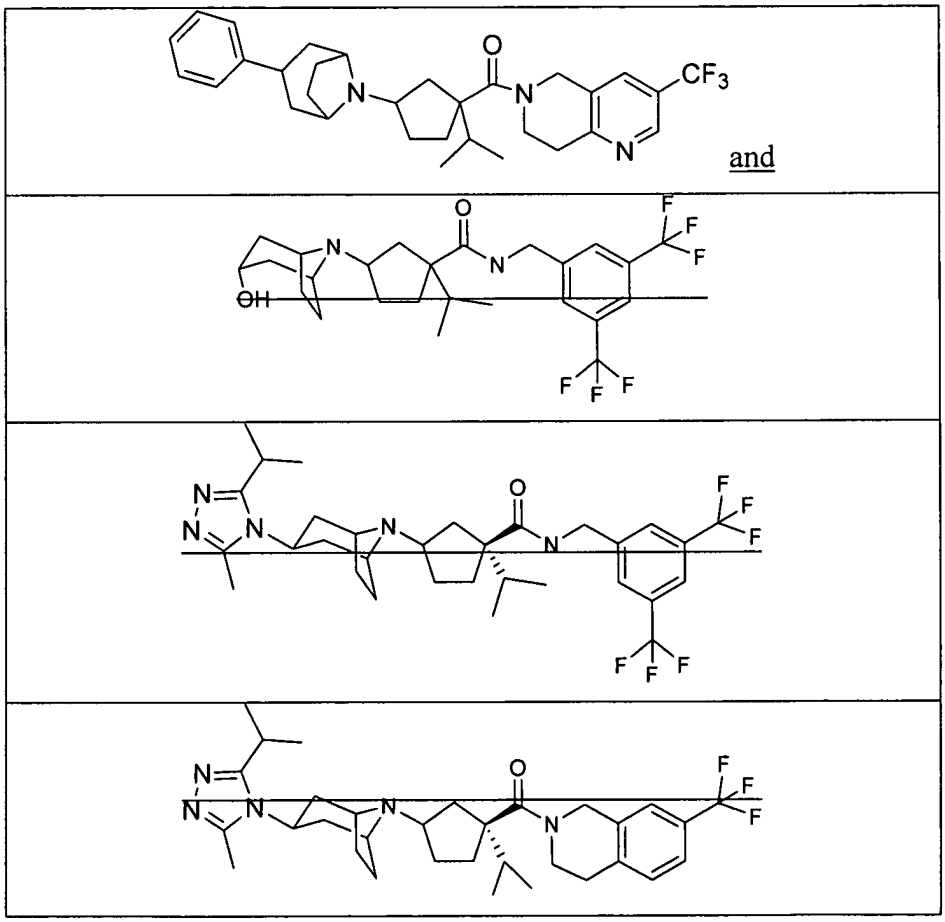
27. (original) The compound of claim 1, wherein R^{16} and R^{18} are joined by $-CH_2-CH_2-$ to make a 5 membered heterocycle, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

28. (original) The compound of claim 1, wherein one or more of R^{19}, R^{20}, R^{21} and R^{22} is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

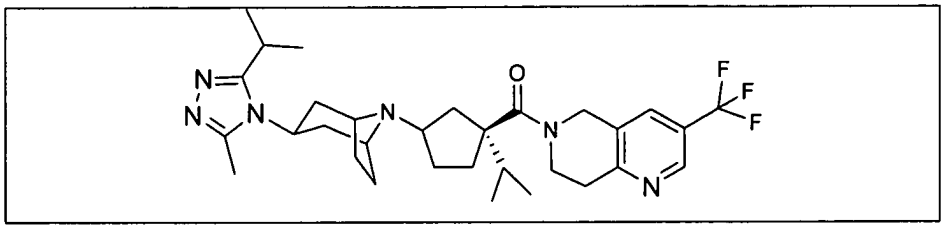
29. (canceled)

30. (original) The compound of claim 1, wherein n is 1, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

31. (currently amended) A compound selected from:



and



and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

32. (original) A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

33. (currently amended) A method for <u>modulation</u> ~~modulations~~ of chemokine receptor activity in a mammal which comprises the administration of an effective amount of a compound of Claim 1.

34. (original) A method for treating, ameliorating, controlling or reducing the risk of an inflammatory and immunoregulatory disorder or disease which comprises the administration to a patient of an effective amount of a compound of Claim 1.

35. (original) A method for treating, ameliorating, controlling or reducing the risk of rheumatoid arthritis which comprises the administration to a patient of an effective amount of a compound of Claim 1.